Efficacy and Safety of Nonantibiotic Outpatient Treatment in Mild Acute Diverticulitis (DINAMO-study)

A Multicentre, Randomised, Open-label, Noninferiority Trial

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Objective: Mild AD can be treated safely and effectively on an outpatient basis without antibiotics.

Summary of Background Data: In recent years, it has shown no benefit of antibiotics in the treatment of uncomplicated AD in hospitalized patients. Also, outpatient treatment of uncomplicated AD has been shown to be safe and effective.

Methods: A Prospective, multicentre, open-label, noninferiority, randomized controlled trial, in 15 hospitals of patients consulting the emergency department with symptoms compatible with AD.

The Participants were patients with mild AD diagnosed by Computed Tomography meeting the inclusion criteria were randomly assigned to control arm (ATB-Group): classical treatment (875/125 mg/8 h amoxicillin/clavulanic acid apart from anti-inflammatory and symptomatic treatment) or experimental arm (Non-ATB-Group): experimental treatment (antiinflammatory and symptomatic treatment). Clinical controls were performed at 2, 7, 30, and 90 days.

The primary endpoint was hospital admission. Secondary endpoints included number of emergency department revisits, pain control and emergency surgery in the different arms.

Results: Four hundred and eighty patients meeting the inclusion criteria were randomly assigned to Non-ATB-Group (n = 242) or ATB-Group (n = 238). Hospitalization rates were: ATB-Group 14/238 (5.8%) and Non-ATB-Group 8/242 (3.3%) [mean difference 2.58%, 95% confidence interval (CI) 6.32 to -1.17], confirming noninferiority margin. Revisits: ATB-Group 16/238 (6.7%) and Non-ATB-Group 17/242 (7%) (mean difference -0.3, 95% CI 4.22 to -4.83). Poor pain control at 2 days follow up: ATB-Group 13/230 (5.7%), Non-ATB-Group 5/221 (2.3%) (mean difference 3.39, 95% CI 6.96 to -0.18).

Conclusions: Nonantibiotic outpatient treatment of mild AD is safe and effective and is not inferior to current standard treatment.

Trial registration: ClinicalTrials.gov (NCT02785549); EU Clinical Trials Register (2016-001596-75)

Keywords: mild acute diverticulitis, nonantibiotic in acute diverticulitis, outpatient in acute diverticulitis

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Incidence of diverticular disease is increasing: approximately 30% of the population older than 45 years and 60% of those over 85 years have diverticula. Approximately 10%–25% of these patients will suffer an episode of acute diverticulitis (AD) at some point in their lifetime.[1] AD is 1 of the most prevalent reasons for consultation to EDs in Western countries.[2] However, 75% of these episodes do not present complications and most will have achieve good outcomes with conservative treatment.[3]

Since its initial description, the treatment of AD has not been based on a solid scientific grounding; it has consisted of hospital admission and antibiotics, assuming an infectious etiology.[3] In recent years, 2 randomized controlled trials have shown no benefit of antibiotics in the treatment of uncomplicated AD in hospitalized patients.[4,5] These studies found no significant differences with regard to time to recovery, complications, recurrences and need for surgery between groups with or without antibiotic treatment, and also suggested that antibiotics could be omitted in patients with a first episode of uncomplicated AD. Similarly, many systematic reviews and meta-analyses support the nonantibiotic treatment of uncomplicated AD,[6,7] and in fact this approach is included in the Guidelines of the American Society of Colon and Rectal Surgeons.[8]

Outpatient treatment of uncomplicated AD has been shown to be safe and effective.[9] No differences have been reported with regard to treatment failure, and the overall health care cost per episode is lower in outpatient group.

The main objective of the study was to establish whether patients treated with or without antibiotics on an outpatient basis would present differences in terms of admission rates. The secondary objectives were to analyse differences with regard to (1) ED revisits (and the reasons for revisit); (2) pain control at various time points; and (3) complication rates.

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A noninferiority design was chosen for the study on the assumption that the new non-antibiotic outpatient treatment regime would not be inferior to the standard treatment with antibiotics and hospital admission.

METHODS

Study Design

The DINAMO-study is a multicentre, prospective, open-label, noninferiority, randomized controlled trial[10] with an intention-to-treat approach and parallel assignment, and with the participation of 15 colorectal surgery units at acute-care secondary and tertiary hospitals throughout Catalonia (Spain). All the institutions belong to the Spanish Public Health System.

The trial was conducted in accordance with the Declaration of Helsinki, seventh revision,[11] the SPIRIT 2013 Standard Protocol Items for Clinical Trials[12] and the Spanish laws and regulations for biomedical research. Authorization was obtained from the Spanish Agency for Medicines and Medical Devices (*Agencia Española del Medicamento y Productos Sanitarios*, AEMPS).

The trial protocol, patient information and informed consent documents were approved by the ethics committees of all participating trial centres in accordance with the Royal Decree 1090/2015 of 4th December. The trial was registered at the ClinicalTrials.gov database (ID: NCT02785549) and the EU Clinical Trials Register database (EudraCT number: 2016-001596-75). The study protocol has been published previously by our team.[10]

Participants

Inclusion criteria: age between 18 and 80 years (inclusive), modified Neff 0 AD on abdominal CT scan, no AD episode in the last 3 months, no antibiotic treatment for any reason in the last 2 weeks, no significant comorbidities, immunocompetence, patient's written informed consent, adequate cognitive capacity, adequate family support, good symptom control at the ED and maximum 1 of the following: T $\geq$ 38°C, T <36°C, L >12,000/μL, L <4000/μL, HR >90 bpm, RR >20 rpm, CPR >15 mg/dL.

Exclusion criteria: women in pregnancy or breastfeeding, age <18 years or > 80 years, allergy to any of the study drugs, modified Neff grade I or upper AD, AD episode in the last 3 months, inflammatory bowel disease, antibiotic treatment for any reason in the last 2 weeks, presence of significant comorbidities, immunodepression, absence of patient's written informed consent, inadequate cognitive capacity, inadequate family support, poor symptom control at the ED (VAS $\geq$ 5) and/or systemic inflammatory response syndrome.

Significant comorbidities were defined as diabetes mellitus with organic involvement (retinopathy, angiopathy, nephropathy), emergency assistance for a cardiogenic event in the last 3 months (acute myocardial infarction, angina, heart failure), decompensation of chronic liver disease in the last 3 months (Child $\geq$ B) and end-stage renal disease. Immunocompetence was defined as the absence, and immunodepression as the presence, of any of the following: active neoplastic disease, hematologic malignancy, human immunodeficiency virus with low CD4+ count (AIDS), long term corticosteroid treatment, immunosuppressant therapy, transplant, splenectomy and genetic immunodeficiency.

"Adequate cognitive capacity" was defined as the ability to read and understand the description of the study and to provide signed informed consent. "Family support" was defined as "adequate" when the patient had someone able to take care of him/her and provide help as necessary.

The diagnosis of AD was performed by abdominal tomography (CT) and the modified Neff classification (mNeff)[13] was applied.[14,15] All eligible patients who were not included in the study were registered and the reasons for their nonparticipation stated in accordance with the Consolidated Standards for Reporting Trials statement for noninferiority and equivalence randomized trials.[16]

Randomization and Masking

Patients visiting the ED with clinical features compatible with AD underwent a blood test and an abdominal CT scan. Once the diagnosis of mild AD was confirmed (grade 0 mNeff), patients meeting the inclusion criteria were invited to take part in the study. On agreeing to participate, they provided written consent by signing a standardized informed consent document and were randomized to 1 of the 2 study arms in a 1:1 allocation ratio. The patients were randomized after successful symptom control in the ED. The study was open-label and no masking of patients or surgeons was performed. At the design stage we considered the possibility of carrying out a single blind antibiotic vs placebo trial, but we decided against this option because of the study's multicentre design.

Procedures

In the Experimental arm (Non-ATB-Group), patients were given anti-inflammatory and symptomatic treatment with 600 mg/8 h ibuprofen alternating with 1 g/8 h acetaminophen. In the Control arm (ATB-Group) patients were treated with 875/125 mg/8 h amoxicillin/clavulanic acid apart from the same anti-inflammatory (NSAIDS) and symptomatic treatment.

Medical treatment was initiated in the ED. The route of administration was EV in the ED, and oral at discharge. Patients were discharged with medical treatment and diet recommendations when they achieved good symptomatic control in the ED. If no good symptomatic control was achieved after a maximum of 24 hours of observation in the ED, patients were admitted for EV treatment and therefore did not enter the study. The duration of medical treatment (with or without antibiotics) was 7 days.

Outcomes

The 2 groups underwent the same clinical controls at 2, 7, 30, and 90 days after the episode, conducted by surgeons of the coloproctology unit. At each control, an overall assessment was made through a physical examination, the clinical evolution was monitored and adherence to the treatment was checked. The degree of pain was recorded at each control on a visual analogue scale (VAS, 0–10). If clinical worsening or poor symptomatic control was detected at any time, the patient was referred to the ED. Patients also consulted the ED if, at their own discretion and based on the information received, they presented any alarm symptoms (temperature > 38°C or poor symptomatic control).

In the event of a revisit to the ED, an abdominal CT scan and a blood test were repeated. The same follow-up (FU) was maintained. The algorithm protocol recommended by the investigators for selecting the most appropriate treatment in the event of a revisit was described in the study protocol.[10]

Sample Size

Based on the results of a previous study by our group, the sample size was calculated taking hospital admission as the main factor.[14] A noninferiority margin of 7% (Δ) for both the ATB-Group and the Non-ATB-Group on the basis of our previous study of outpatient treatment of AD, in which we obtained a success rate of 93%.[14] Using 80% power and a 1-sided significance level of 0.025. With an estimated patient loss of 10%, we concluded that a sample size of 230 patients per arm was required for the study.

Statistical Analysis

The primary endpoint was analysed by both intention-to treat and per protocol analysis, because all randomized patients received

treatment. The description of the factors and the statistical analysis were performed using the Statistical Package for the Social Sciences program (SPSS Inc., Chicago, IL) version 26.

The quantitative variables were described using values of means and standard deviation when the distribution was considered normal (Kolmogorov-Smirnov test), otherwise using the values of the median and interquartile range (IQR). The categorical variables are described in absolute numbers and in percentages.

The univariate statistical analysis of the quantitative variables, with independent groups, was performed using the Student *t* test if its application conditions were fulfilled; otherwise, the Mann-Whitney *U* test was applied. For categorical variables, the Pearson χ^2 test was used. The results of the statistical tests are shown with a 95% confidence interval (CI) whenever possible. Statistical significance was set at a *P* value below 0.05.

We determined a 95% CI of the difference for the primary endpoint (one-sided 5% α level). Thus, noninferiority was concluded if the lower bound of this interval was below the noninferiority limit (Δ=7%).

The revisit to ED factor was analyzed with the Kaplan-Meier estimation method and the log-rank test.

RESULTS

Participant Flow and Recruitment

From November 2016 to January 2020, 849 patients diagnosed with mild AD (grade 0 mNeff)[13] were seen at the ED of the hospitals participating in the study. Four hundred and eighty patients with AD meeting the inclusion criteria were randomly assigned to the Non-ATB-Group (n = 242) or the ATB-Group (n = 238) (Fig. 1). In baseline characteristics of patients, no statistically significant differences were found between groups, except between CRP values, but they were not clinically relevant (Table 1).

Main Objective: Admission to Hospital

Revisits to the ED resulted in 22/480 (4.6%) admissions: 14/238 (5.8%) in ATB-Group and 8/242 (3.3%) in Non-ATB-Group, with a 2.58% difference (95% CI 6.32 to -1.17), (p = 0.19). Non-ATB-Group showed noninferiority when compared to ATB-Group, with $\Delta < 7\%$ (Fig. 2A). Most of the admissions were based on the study protocol recommendations upon revisit. However, the final decision regarding admission was taken by the physician.

All patients who revisited the ED underwent an abdominal CT scan (Fig. 1). In the ATB-Group, from the 14 patients admitted to hospitalization, 78.6% (11/14) had mNeff grade 0 AD and 21.4% (3/14) grade Ib. In the Non-ATB-Group, from the 8 patients admitted to hospitalization, 87.5% (7/8) had mNeff grade 0 AD and 12.5% (1/8) grade Ia.

In the ATB-Group, the same antibiotic, amoxicillin/clavulanic acid, was maintained in 57.1% (8/14) although in the other 42.8% (6/14) the antibiotic spectrum was widened. In Non-ATB-Group, all admitted patients were treated with amoxicillin/clavulanic acid. Median duration of the admission was 5 days in the ATB-Group (IQR 3 days) and 2.5 days in the Non-ATB-Group (IQR 3 days) (P = 0.002), a statistically significant difference. None of the patients in either group required emergency surgery.

Secondary Objectives

Revisit

During the study period, 447 patients did not return to the ED. However, 40/480 (8.3%) revisits were recorded corresponding to 33 patients: 16/238 (6.72%) in the ATB-Group and 17/242 (7.02%) in the Non-ATB-Group (mean difference -0.3, 95% CI 4.22 to -4.83). A total of 29 patients revisited ED once (14 ATB-Group and 15 Non-ATB-Group), 2 patients revisited twice (both Non-ATB-Group), one ATB-Group patient revisited 3 times and another ATB-Group patient revisited 4 times. Fig. 2B shows the number of patients who revisited the ED referred by the physician in each of the clinical controls and the patients who were subsequently admitted to hospital. Fig. 3 displays the revisits to the ED and measures taken. In the ATB-Group, 21 revisits were recorded corresponding to 16 patients and in the Non-ATB-Group, 19 revisits corresponding to 17 patients. In 11/19 (57.9%) there was no worsening of the complementary tests and patients could be kept under the same treatment (that is, NSAIDs on an outpatient basis).

We found no statistically significant differences between groups in any of the factors studied in patients who revisited the ED (Table 2). Interestingly, there were more admissions to hospital in the ATB-Group (14/21, 66.6%) than in the Non-ATB-Group (8/19, 42.1%). A therapeutic change (either starting antibiotic treatment or broadening the spectrum) was needed in 6 out of 21 (28.5%) ATB-Group patients and in 8 out of 19 (42.1%) Non-ATB-Group patients, although the differences were not statistically significant. The median time to revisit was 17 days in the ATB-Group (95% CI: 0 to 36.4) and 13 days in the Non-ATB-Group (95% CI: 4.5 to 25.5), with no statistically significant differences in the log-rank test (P = 0.82) (Fig. 4).

Follow-Up, Pain Control and Recovery

At the end of the study period, there were 22/238 (9.2%) losses to FU in the ATB-Group group and 19/242 (7.9%) in the Non-ATB-Group group (Fig. 2C). The analysis made of remaining patients showed no statistically significant differences between groups in terms of clinical evolution, pain control and consultation to ED recommended by a physician. At 30-day FU, 212/216 ATB-Group patients (98.1%) and 218/223 Non-ATB-Group patients (97.7%) presented good clinical evolution and were able to eat a normal diet.

Patients in the ATB-Group showed a higher degree of pain at the 2-day clinical control, 13/230 (5.7%), Non-ATB-Group 5/221 (2.3%) (mean difference 3.39, 95% CI 6.96 to -0.18). Patients in the Non-ATB-Group recorded higher pain scores at later controls: the differences were not statistically significant (Fig. 2D).

Complications

No patients in either group needed emergency surgery during the study period.

DISCUSSION

Diverticular disease has a high prevalence, especially in the western world, and between 15% and 20% of the population with diverticulosis present complicated AD.[1] Three-quarters of cases of AD are mild.[2] The gold standard test for AD, in addition to the medical history and physical examination, is CT,[3] which allows differential diagnosis and optimal classification. In our study we used the Neff classification, modified by the incorporation of substage Ia to characterize AD with localized pneumoperitoneum.[13] This classification allows us to differentiate between the initial stages of AD and to establish the appropriate treatment at each stage.

''Hospital admission'' was considered as the main factor because it allowed us to assess the safety of outpatient care and the likelihood of treatment failure in mild AD. The delta margin was based on the results of our previous study, which achieved a success rate of 93% in the outpatient protocol for the treatment of uncomplicated AD.[14] The dose and duration of treatment in the 2 arms (ATB-Group: antibiotic and Non-ATB-Group: anti-inflammatory) were prescribed using the outpatient treatment protocols in the antibiotic group applied in previous studies.[14,15]

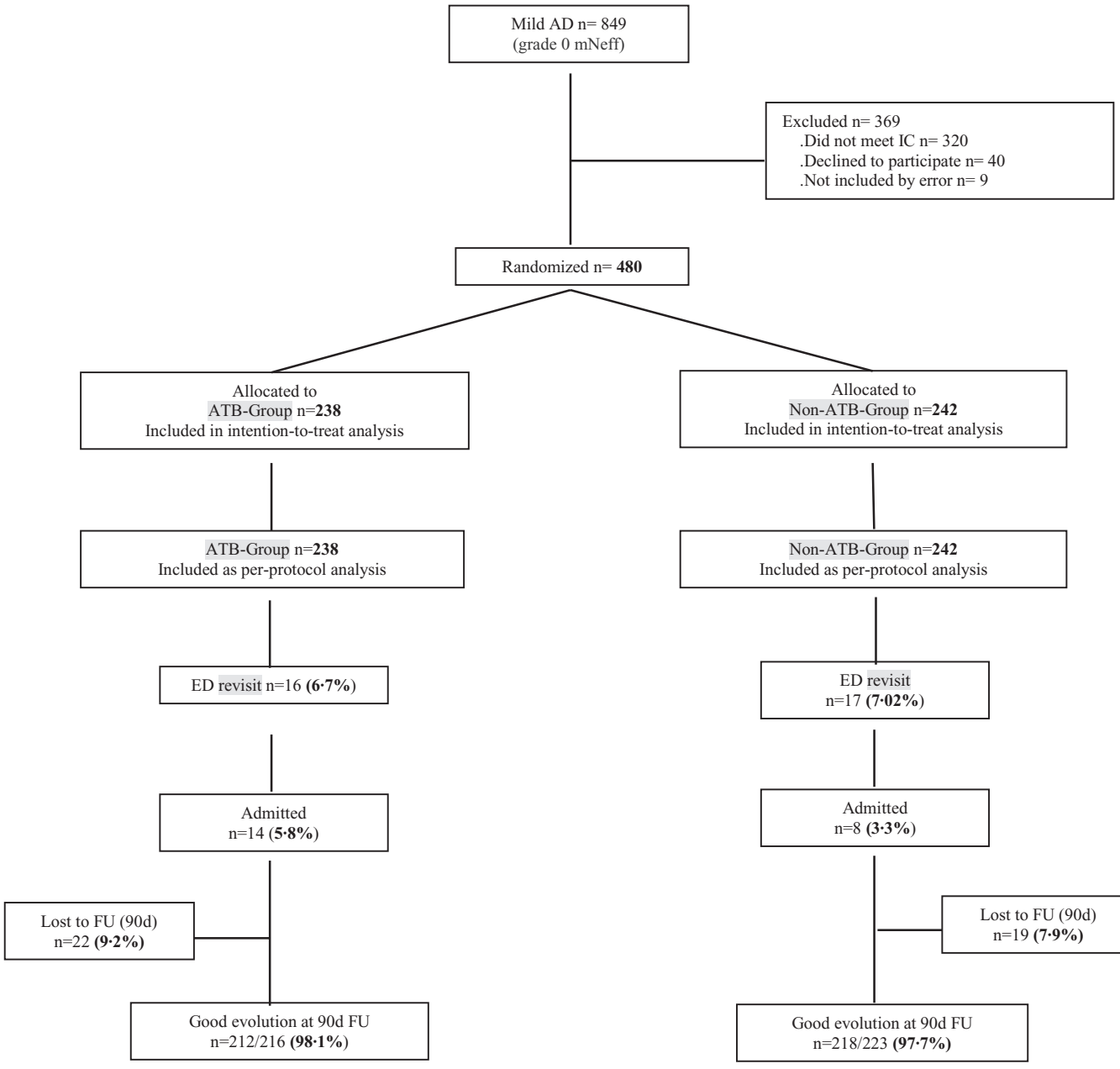


FIGURE 1. CONSORT diagram. AD, acute diverticulitis; d, days; ED, emergency department; FU, follow-up; IC, inclusion criteria; mNeff, modified Neff CT-scan classification.

Two randomized controlled trials have already reported non-antibiotic treatment of uncomplicated AD,[4,5] but neither was performed on an outpatient basis. With follow-up periods of 12 months, Daniels et al[4] and Chabok et al[5] demonstrated that antibiotic-free treatment does not worsen complications, cause recurrences, or delay complete recovery. As a result, in our study design we considered that a follow-up of more than 90 days was unnecessary to estimate the recovery time.

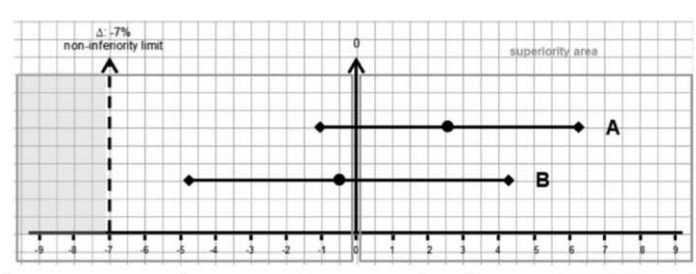
The results of our outpatient treatment regimen show that it is a safe and effective option. Sixteen out of 238 (6.72%) patients in the antibiotic group revisited the ED compared with 17/242 (7.02%) in the nonantibiotic group, and 14 out of 238 (5.8%) in the antibiotic group required hospitalization, compared with 8 out of 242 (3.3%) in the nonantibiotic group; the differences were not statistically significant, and the 95% confidence intervals were far from the non-inferiority margin. These results are similar to those recorded in the DIVER study.[10] In that study, the primary endpoint was treatment failure, which was recorded in 4 out of 66 patients (6.1%) in the admitted group and in 3 out of 66 (4.5%) in the outpatient group ($p = 0.619$). The overall number of admissions in our study was 22/480 (4.6%), similar to the rates in the DIVER study[8] (6.1%) and in our previous study (64/68, 6%).[13]

The 40 ED revisits (a rate of 8.3%) were distributed evenly between the 2 groups: 21 (8.8%) in the ATB-Group and 19 (7.8%) in

TABLE 1. Baseline Characteristics of Patients According to Study Group

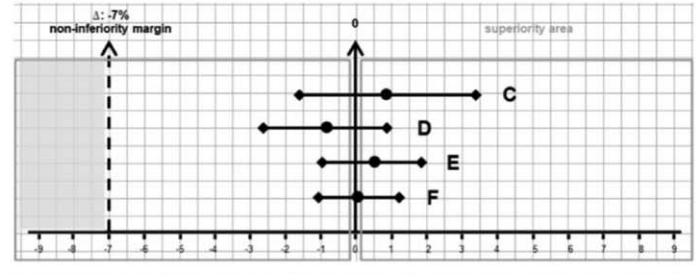
	ATB-Group (n = 238)	Non-ATB-Group (n = 242)	*P*
Age (yr) / Median (IQR)	57 / (19)	59 / (18)	0.13*
Gender (male: female)	120:118	104:138	0.12^
Temperature (°C)/ Median (IQR)	36.3/(0.7)	36.4 / (0.8)	0.63’
Respiratory rate (rpm)/Median (IQR)	21/(0)	21 / (1)	0.07*
Heart rate (bpm)/ Median (IQR)	80/(16)	80 / (15)	0.31*
CRP (mg/dL)/ Median (IQR)	4.4/(5.5)	5.1 / (6.5)	0.01*
Leucocytosis (U/μL) /Mean (SD)	10,691/(2979)	10,822 / (3,023)	0.63*
Pain (VAS)/Median (IQR)	5/(3)	4 / (2)	0.07*

Figures shown are averages except for gender.
ATB-Group indicates control arm; CRP, C-reactive protein; IQR, interquartile range; Non-ATB-Group, experimental arm; SD, standard deviation; VAS, visual analogue scale.
*Mann-Whitney *U* test.
^Fisher exact test.
’*T*-Test.



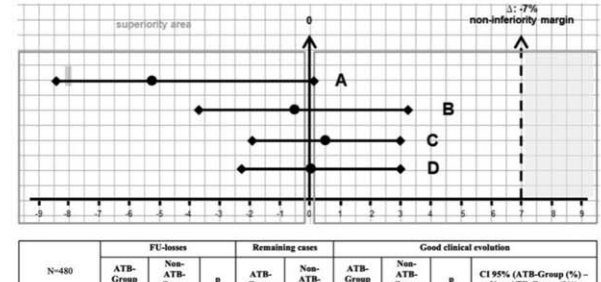
90-days FU	ATB-Group (%)	Non-ATB-Group (%)	p	CI 95% (ATB-Group (%) – Non-ATB-Group (%))
(A) Admission	14/238 (5·8%)	8/242 (3·3%)	0·19	2·58 (6·32 to -1·17)
(B) ED revisit	16/238 (6·7%)	17/242 (7%)	1	-0·3 (4·22 to -4·83)

A



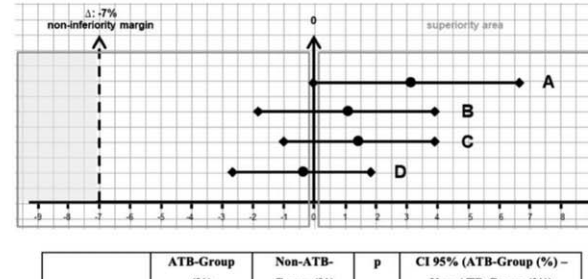
ED revisit referred by surgeon	ATB-Group (%)	Non-ATB-Group (%)	p	CI 95% (ATB-Group (%) – Non-ATB-Group (%))
(C) 2-days FU	6/230 (2·6%)	4/221 (1·8%)	0·75	0·8 (3·51 to -1·91)
(D) 7-days FU	1/208 (0·5)	3/219 (1·4%)	0·62	-0·89 (0·91 to -2·69)
(E) 30-days FU	2/225 (0·9%)	1/224 (0·4%)	1	0·44 (1·95 to -1·06)
(F) 90-days FU	1/216 (0·2%)	1/223 (0·2%)	1	0·01 (1·27 to -1·25)

B



N=480	FU-losses			Remaining cases		Good clinical evolution			
	ATB-Group (%)	Non-ATB-Group (%)	p	ATB-Group	Non-ATB-Group	ATB-Group (%)	Non-ATB-Group (%)	p	CI 95% (ATB-Group (%) – Non-ATB-Group (%))
(A) 2-days FU	8 (3·4%)	21 (8·7%)	0·02	230	221	221 (91·7%)	212 (95·9%)	0·79	-4·19 (0·22 to -8·6)
(B) 7-days FU	30 (12·6%)	23 (9·5%)	0·31	208	219	201 (96·6%)	212 (96·8%)	1	-0·17 (3·2 to -3·6)
(C) 30-days FU	13 (5·5%)	18 (7·4%)	0·46	225	224	220 (97·8%)	217 (96·9%)	0·58	0·9 (3·0 to -2·1)
(D) 90-days FU	22 (9·2%)	19 (7·9%)	0·63	216	223	212 (98·1%)	218 (97·7%)	1	0·4 (3·04 to -2·3)

C



	ATB-Group (%)	Non-ATB-Group (%)	p	CI 95% (ATB-Group (%) – Non-ATB-Group (%))
(A) 2-days FU	13/230 (5·7%)	5/221 (2·3%)	0·09	3·39 (6·96 to -0·18)
(B) 7-days FU	6/208 (2·9)	4/219 (1·8%)	0·53	1·06 (3·9 to -1·8)
(C) 30-days FU	6/225 (2·7%)	3/224 (1·3%)	0·34	1·3 (3·9 to -1·3)
(D) 90-days FU	3/216 (1·4%)	4/223 (1·8%)	1	-0·4 (1·9 to -2·7)

D

FIGURE 2. Differences in admission to hospital and revisit to Emergency Department (ED) between treatment arms Error bars indicate 2-sided 95% CIs. The dashed arrow at x = Δ indicates the noninferiority margin. The bold arrow indicates the zero. The region to the left of x = Δ indicates the zone of inferiority. Calculations are made considering Follow Up (FU)-losses at each time point. 2A. A- Patients admitted to hospital after revisit to ED during the 90-day FU period. B- Patients who revisited ED during the 90-day FU period. 2B. Patients referred to ED by the surgeon at each clinical control: C- 2-days, D- 7-days, E- 30-days, F- 90 days. ATB-Group, control arm; CI, confidence interval; ED, emergency department; FU, follow-up; Non-ATB-Group, experimental arm. 2C: Patients with good clinical outcome during follow-up. Error bars indicate 2-sided 95% CIs. The dashed arrow at x = Δ indicates the noninferiority margin. The bold arrow indicates zero. The region to the right of x = Δ indicates the zone of inferiority. Calculations are made considering FU-losses at each time point. *Good clinical evolution* was defined as good pain control, good oral tolerance to the diet (liquids, low-fibre or normal) and normal abdominal palpation. ATB-Group, control arm; CI, confidence interval; FU, follow-up; Non-ATB-Group, experimental arm. 2D: Patients with poor pain control in each treatment arm along the study period. Error bars indicate 2-sided 95% CIs. The dashed arrow at x = Δ indicates the noninferiority margin. The bold arrow indicates the zero. The region to the left of x = Δ indicates the zone of inferiority. Calculations are made considering FU-losses at each time point. Poor pain control was defined as VAS ≥ 5. ATB-Group, control arm; CI, confidence interval; ED, emergency department; FU, follow-up; Non-ATB-Group, experimental arm.

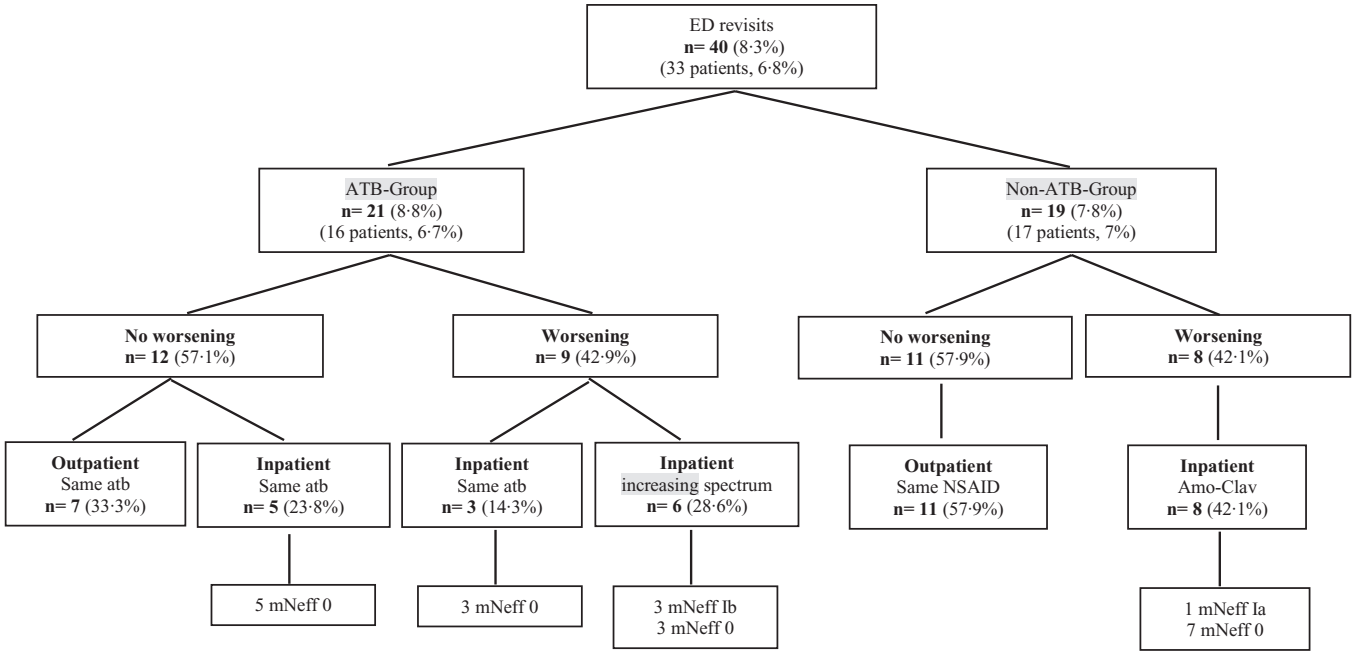


FIGURE 3. Revisits to the ED and attitude taken. During the study period there were 40 revisits to the ED in 33 patients: 29 patients revisited once, 2 patients revisited twice, 1 patient revisited 3 times and 1 patient revisited 4 times to the ED. 447 patients did not revisit ED. Amo-Clav, amoxicillin/clavulanic acid; atb, antibiotic; ED, emergency department; mNeff, modified Neff CT-scan classification; NSAID, non-steroidal anti-inflammatory drugs.

the Non-ATB-Group group. In all cases, analytical tests and control CT were performed to rule out worsening. Poor symptom control was recorded in 12/21 (57.1%) of the ATB-Group and in 11/19 (57.9%) of the Non-ATB-Group. In the Non-ATB-Group, the same antibiotic was maintained in all cases and was administered in-hospital on 5 occasions: all these cases in the Non-ATB-Group group were discharged again with anti-inflammatory treatment. Analytical or radiological worsening was detected in 9/21 (42.9%) of the ATB-Group and in 8/19 (42.1%) of the Non-ATB-Group. In the ATB-Group, all patients were admitted; in 3 cases the same treatment was maintained and in the other 6 it was changed to a more powerful antibiotic. In the Non-ATB-Group, all 8 cases were admitted and antibiotic treatment was started. Only 3 patients in the ATB-Group presented radiological deterioration to mNeff grade Ib, and 1 patient in the Non-ATB-Group was seen to have progressed to mNeff grade Ia on the control CT at the consultation. None of the consultations required emergency surgery or any measures other than hospital admission or change of antibiotic treatment. So we can say that the action protocol described in the DINAMO study is safe and does not represent an increased risk.

None of the follow-up controls carried out at outpatient clinics reached the limit of noninferiority for patient referral (Fig. 2B). In addition, there were no differences between groups in terms of pain control in any of the controls up to 90 days, nor in relation to clinical evolution.

The main limitation of the study is the significant number of patients excluded, due to the application of strict selection criteria. This high proportion is due to the fact that the patients were to be

TABLE 2. Characteristics of Patients who Revisited ED

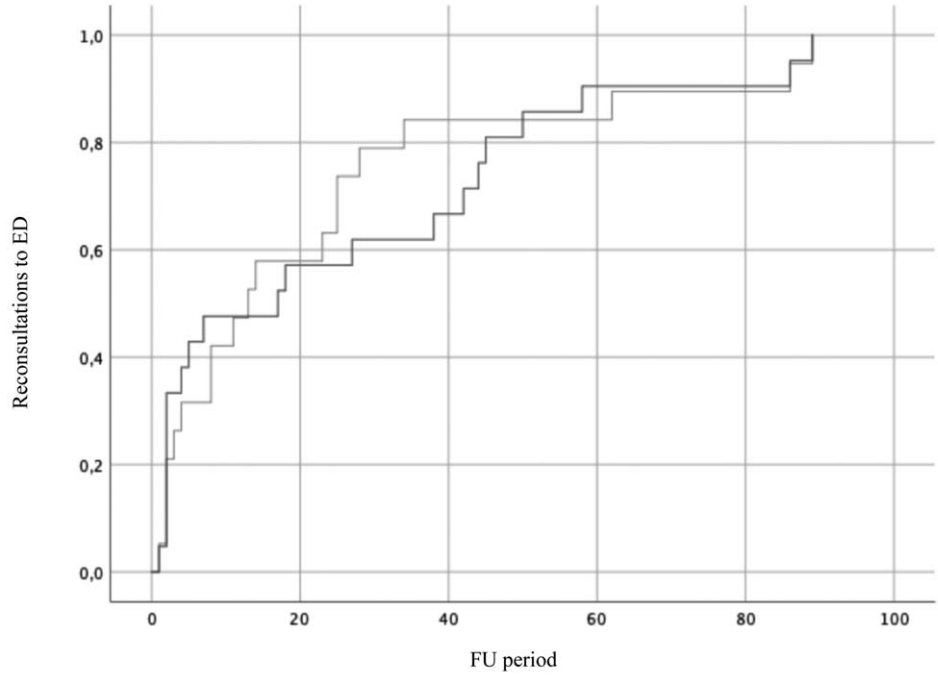
	ATB-Group (%) 21 (52.5)	Non-ATB-Group (%) 19 (47.5)	95% CI (CA (%) – EA (%))	*P*
Days to revisit / Median (IQR)	17 / (43)	13 / (25)	..	0.98
T°≥38°C	1 (4.8)	2 (10.5)	−5.8 (10.8 to 22.3)	0.6
CRP ≥15 mg/dl	4 (19)	0	19 (35.9 to 2.3)	0.1
Leucocytosis ≥12000/μL	8 (38.1)	7 (36.8)	1.25 (31.3 to −28.8)	1
Higher VAS*	16 (76.2)	11 (57.9)	18.3 (47 to −10.4)	0.31
Admitted to hospital	14 (66.6)	8 (42.1)	20.3 (58.8 to −0.11)	0.11
Medical treatment upgrade†	6 (28.6)	8 (42.1)	−13 (15.9 to −43)	0.51

Calculations are based on 21 revisits in **ATB-Group** and 19 revisits in **Non-ATB-Group**.

*Patients who had the same or more pain in the revisit to the ED compared with the initial ED evaluation.

†Initiating antibiotic in **Non-ATB-Group** or widening spectrum of antibiotic in **ATB-Group**.

ATB-Group indicates control arm; CI, confidence interval; CRP, C-reactive protein; ED, emergency department; IQR, interquartile range; **Non-ATB-Group**, Experimental arm; T°, temperature; VAS, visual analogue scale.



Days	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
Non-ATB-Group	0	6	8	11	11	14	15	16	16	16	16	16	16	17	17	17	17	17	19
ATB-Group	0	9	10	10	12	12	13	13	14	17	18	18	18	18	18	18	18	18	21

FIGURE 4. Kaplan-Meier cumulative incidence of revisits to the ED in each treatment arm over the study period. Red line: ATB-Group. Blue line: Non-ATB-Group. ATB-Group, control arm; ED, emergency department; FU, follow-up; Non-ATB-Group, experimental arm.

selected for outpatient treatment, and so, to ensure high levels of safety, restrictive criteria had to be applied. The DIABOLO study[4] also excluded a high number of patients: 323 of the 893 possible candidates (36.2%). In addition, since the physicians in the trial were involved in the decisions regarding hospital admission (the primary outcome factor) there may also have been some observer/selection bias. Another limitation has been the lack of use of placebo. However, the high complexity of its control, in a multicenter study, made us reject this procedure

It is also true that some guidelines such as those of the American Society of Colon and Rectal Surgeons[8] already accept the non-use of antibiotics in the cases of healthy patients with uncomplicated diverticulitis. Some other studies[16] also administer outpatient treatment without antibiotics for AD. However, the research described here is the first prospective, multicentre, randomized study to attempt to demonstrate the noninferiority of outpatient nonantibiotic treatment of mild diverticulitis. We believe that our results can be extrapolated to populations of any kind and that episodes of uncomplicated AD can be treated on an outpatient basis and without antibiotics, provided that well-defined clinical and radiological criteria are applied.

In conclusion, the DINAMO study demonstrates that antibiotic-free outpatient treatment of mild AD is not inferior to standard antibiotic treatment in terms of hospital admission, revisit rates, or subsequent recovery. There were no additional complications or serious adverse effects compared with the current standard treatment. Therefore, this is a safe and effective therapeutic approach that can be considered as routine practice, offering the economic advantages of outpatient care and the practical advantages of the avoidance of antibiotic treatment.

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JAMA Surgery | Original Investigation

Diagnostic Accuracy of Radioactive Iodine Seed Placement in the Axilla With Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy in Node-Positive Breast Cancer

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IMPORTANCE Several less-invasive staging procedures have been proposed to replace axillary lymph node dissection (ALND) after neoadjuvant chemotherapy (NAC) in patients with initially clinically node-positive (cN+) breast cancer, but these procedures may fail to detect residual disease. Owing to the lack of high-level evidence, it is not yet clear which procedure is most optimal to replace ALND.

OBJECTIVE To determine the diagnostic accuracy of radioactive iodine seed placement in the axilla with sentinel lymph node biopsy (RISAS), a targeted axillary dissection procedure.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective, multicenter, noninferiority, diagnostic accuracy trial conducted from March 1, 2017, to December 31, 2019. Patients were included within 14 institutions (general, teaching, and academic) throughout the Netherlands. Patients with breast cancer clinical tumor categories 1 through 4 (cT1-4; tumor diameter <2 cm and up to >5 cm or extension to the chest wall or skin) and pathologically proven positive axillary lymph nodes (ie, clinical node categories cN1, metastases to movable ipsilateral level I and/or level II axillary nodes; cN2, metastases to fixed or matted ipsilateral level I and/or level II axillary nodes; cN3b, metastases to ipsilateral level I and/or level II axillary nodes with metastases to internal mammary nodes) who were treated with NAC were eligible for inclusion. Data were analyzed from July 2020 to December 2021.

INTERVENTION Pre-NAC, the marking of a pathologically confirmed positive axillary lymph node with radioactive iodine seed (MARI) procedure, was performed and after NAC, sentinel lymph node biopsy (SLNB) combined with excision of the marked lymph node (ie, RISAS procedure) was performed, followed by ALND.

MAIN OUTCOMES AND MEASURES The identification rate, false-negative rate (FNR), and negative predictive value (NPV) were calculated for all 3 procedures: RISAS, SLNB, and MARI. The noninferiority margin of the observed FNR was 6.25% for the RISAS procedure.

RESULTS A total of 212 patients (median [range] age, 52 [22-77] years) who had cN+ breast cancer underwent the RISAS procedure and ALND. The identification rate of the RISAS procedure was 98.2% (223 of 227). The identification rates of SLNB and MARI were 86.4% (197 of 228) and 94.1% (224 of 238), respectively. FNR of the RISAS procedure was 3.5% (5 of 144; 90% CI, 1.38-7.16), and NPV was 92.8% (64 of 69; 90% CI, 85.37-97.10), compared with an FNR of 17.9% (22 of 123; 90% CI, 12.4%-24.5%) and NPV of 72.8% (59 of 81; 90% CI, 63.5%-80.8%) for SLNB and an FNR of 7.0% (10 of 143; 90% CI, 3.8%-11.6%) and NPV of 86.3% (63 of 73; 90% CI, 77.9%-92.4%) for the MARI procedure. In a subgroup of 174 patients in whom SLNB and the MARI procedure were successful and ALND was performed, FNR of the RISAS procedure was 2.5% (3 of 118; 90% CI, 0.7%-6.4%), compared with 18.6% (22 of 118; 90% CI, 13.0%-25.5%) for SLNB ($P < .001$) and 6.8% (8 of 118; 90% CI, 3.4%-11.9%) for the MARI procedure ($P = .03$).

CONCLUSIONS AND RELEVANCE Results of this diagnostic study suggest that the RISAS procedure was the most feasible and accurate less-invasive procedure for axillary staging after NAC in patients with cN+ breast cancer.

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Patients with clinically node-positive (cN+) breast cancer are often treated with neoadjuvant chemotherapy (NAC). As a result of NAC, approximately one-third of patients with cN+ breast cancer convert to a pathologic complete response (pCR) of the axilla.[1] The axillary pCR rate depends on subtype and may be as high as 74% in *ERBB2* (formerly *HER2* or *HER2/neu*)-positive breast cancer.[2-4] Until recently, patients with cN+ breast cancer were routinely treated with axillary lymph node dissection (ALND), irrespective of treatment response. However, patients with cN+ breast cancer who achieve axillary pCR are not expected to benefit from ALND.

Over the past years, several less-invasive staging procedures have been proposed to enable response-based management of the axilla in patients with cN+ breast cancer: sentinel lymph node biopsy (SLNB),[5-7] excision of the pretreatment-marked positive lymph node (eg, marking axillary lymph node with radioactive iodine seed [MARI] procedure),[8,9] and procedures combining SLNB and excision of the pretreatment-marked positive lymph node (eg, targeted axillary dissection).[10,11] However, these procedures are of varying accuracy and may fail to detect chemotherapy-resistant residual axillary disease compared with ALND, although it is yet unclear whether this affects prognosis. Therefore, the preferred procedure to replace ALND should be the one with the lowest risk of missing residual axillary disease, ie, the number of false-negative results should be as small as possible.

In a meta-analysis[1] including 17 studies on the diagnostic accuracy of SLNB in patients with cN+ breast cancer treated with NAC, the overall false-negative rate (FNR) was 17%. The negative predictive value (NPV) was 86% at best, which means residual axillary disease is missed in at least 1 in 6 patients with tumor-free SLNs. The MARI procedure was developed as an alternative to SLNB: the pathologically proven positive lymph node is marked with a radioactive iodine seed before NAC and excised after NAC. In a single-center prospective trial of 100 patients with cN+ breast cancer, the MARI procedure was associated with an FNR of 7% and an NPV of 83.3%.[8] Thus, residual axillary disease may still be missed in cases of a tumor-free MARI node. Three trials[10,12,13] evaluated the diagnostic accuracy of targeted axillary dissection: the FNR ranged from 2% to 4%, and the NPV ranged from 92% to 97%. These results are promising, but evidence is limited owing to their study designs and relatively small sample sizes, ranging from 35 to 85 patients.

This prospective, multicenter trial was designed to determine the diagnostic accuracy of the combination of SLNB and MARI, referred to as the radioactive iodine seed placement in the axilla with sentinel lymph node biopsy (RISAS) procedure, for axillary staging after NAC in patients with cN+ breast cancer. The study protocol has been published previously.[14] It was hypothesized that the RISAS procedure would be noninferior to ALND for axillary staging and superior to the separate SLNB and MARI procedure.

Key Points

Question What is the diagnostic accuracy of targeted axillary dissection after neoadjuvant chemotherapy in patients who have clinically node-positive breast cancer?

Findings In this multicenter diagnostic study including 212 patients, the false-negative rate of targeted axillary dissection (ie, radioactive iodine seed placement in the axilla with sentinel lymph node biopsy [RISAS] procedure) was 3.5%. The negative predictive value was 92.8%, meaning that residual disease was missed in only 1 of 14 patients with a pathologic complete response in the RISAS nodes.

Meaning These findings suggest the potential for worldwide implementation of targeted axillary dissection to enable response-based management of the axilla and to guide adjuvant (systemic) treatment strategies.

Methods

Study Design

The RISAS trial was a single-group, prospective, multicenter validation trial. The primary objective was to determine the diagnostic accuracy of SLNB combined with the MARI procedure for axillary staging after NAC in patients with cN+ breast cancer. Secondary objectives included the accuracy of the SLNB and the MARI procedure separately. The medical ethics review committee of the Erasmus Medical Center (Rotterdam, the Netherlands) approved this study, and written informed consent was obtained from all patients. Fourteen institutions participated in this trial, of which 13 institutions actively accrued patients. The review boards of all participating centers approved trial participation. All participating institutions had prior experience with the use of iodine seeds for localization of breast lesions. The trial was registered on ClinicalTrials.gov[15] and was funded by the Dutch Cancer Society. This study followed the Standards for Reporting of Diagnostic Accuracy (STARD) reporting guidelines.

Eligibility Criteria

Female patients 18 years or older were eligible for the study. In addition, patients with breast cancer clinical tumor categories 1 through 4 (cT1-4; tumor diameter <2 cm and up to >5 cm or extension to the chest wall or skin) and clinical node categories cN1 (metastases to movable ipsilateral level I and/or level II axillary nodes), cN2 (metastases to fixed or matted ipsilateral level I and/or level II axillary nodes), or cN3b (metastases to ipsilateral level I and/or level II axillary nodes with metastases to internal mammary nodes) and who were treated with NAC were eligible for inclusion. Nodal positivity had to be confirmed with either fine-needle aspiration cytology or core-needle biopsy before NAC. Patients with positive infraclavicular or supraclavicular lymph nodes, patients with (oligo) metastatic breast cancer, and patients with prior surgery or radiotherapy to the ipsilateral axilla (including SLNB before NAC) were excluded. Patient race and ethnicity data were not gathered for this study; it was not hypothesized that race or ethnicity would be associated with the diagnostic accuracy of the investigated procedure.

Neoadjuvant Chemotherapy

Recommendations for systemic therapy regimens were based on national guidelines. NAC generally included anthracycline- and/or taxane-based regimens. In patients with *ERBB2*-

positive breast cancer, *ERBB2*-targeted therapy (trastuzumab with or without pertuzumab) was added to the chemotherapy regimen.

The RISAS Procedure

The RISAS procedure consisted of both the SLNB and the MARI procedure. Before NAC, patients underwent ultrasound-guided placement of a radioactive iodine seed within the pathologically proven positive lymph node. The seeds labeled with radioactive iodine I 125 (^{125}I) had a maximum activity of 7.4 MBq and a half-life of 60 days. If multiple lymph nodes were suspicious, the lymph node with the most suspicious morphology on ultrasonography was marked. In 1 institution, a protocol deviation took place regarding iodine seed placement: in a small subset of patients, a clip instead of an iodine seed was placed before NAC followed by iodine seed placement after NAC. The study protocol recommended dual-tracer technique for SLNB, but this was not obligated. If a radioactive tracer was used, technetium Tc 99m nanocolloid was injected on the day of or on the day before the surgical procedure followed by lymphoscintigraphy. If blue dye was used, this was injected at the start of the operation and followed by massage of the injection site. The protocol did not require a minimum number of lymph nodes to be excised for the RISAS procedure. Excision of the lymph node containing the iodine seed was confirmed with a gamma probe and/or a specimen radiograph. All hot and/or blue lymph nodes were considered SLNs. Non-SLNs, such as palpable suspicious lymph nodes, were removed at the discretion of the surgeon. During the operation, the RISAS procedure was followed by ALND.

Histopathologic Evaluation

All lymph nodes were stained with hematoxylin and eosin and the pathology outcome was reported separately for the lymph node containing the iodine seed, the SLN(s), and the remaining lymph nodes of the ALND specimen. Axillary pCR was defined as the absence of residual disease, including the absence of isolated tumor cells and micrometastases. On-site use of immunohistochemistry (IHC) was not mandatory. Slides of the RISAS lymph nodes that were considered negative after on-site evaluation were centrally reviewed by a single pathologist (P.J.v.D.). In cases with less than 3 to 5 levels examined, additional sectioning up to the fifth level was done. IHC was performed on all levels (in case this was not performed on-site, including the additional levels).

Power and Sample Size Calculation

This trial was set up to determine if the RISAS procedure would be noninferior to the criterion standard, ALND. The null hypothesis of inferiority would be rejected at a significance level of 5% if the upper bound of the 2-sided 90% Clopper-Pearson CI of the observed FNR was below the noninferiority margin of 6.25%. This margin was considered clinically acceptable as it is far below the threshold of 10% that is generally considered for SLNB. For example, if 144 included patients had a positive ALND, the null hypothesis of inferiority could be rejected if the number of FN results was less than or equal to 4 (FNR 2.78%; 90% CI, 0.95%-6.24%). Assuming an FNR of 2%, a prevalence of a positive ALND of 64%, and a 10% dropout rate, a sample size of 248 patients was needed (with 84% power to reject the null hypothesis). An FNR of 6.25% (the noninferiority margin) corresponded to a NPV of 90%.

Statistical Analysis

The identification rate, the FNR, and the NPV were calculated for the RISAS procedure and for the SLNB and the MARI procedure separately. The identification rate was defined as the number of patients in whom the procedure was successful divided by the total number of patients in whom the procedure was attempted. The procedure was considered successful if at least 1 lymph node could be identified (an SLN and/or a MARI node). All SLN(s) and/or MARI nodes together were considered RISAS lymph nodes. If the surgeon identified a supposed SLN or MARI node, but no lymph node could be identified by the pathologist (eg, only subcutaneous tissue was found), the procedure was recorded as unsuccessful. The MARI node was considered to be an SLN if the surgeon documented that the MARI node was hot and/or blue or if the pathologist documented that the MARI node was blue. If the iodine seed appeared to be located in another lymph node than initially reported by the surgeon, the lymph node containing the iodine seed identified by the pathologist was recorded as the MARI node.

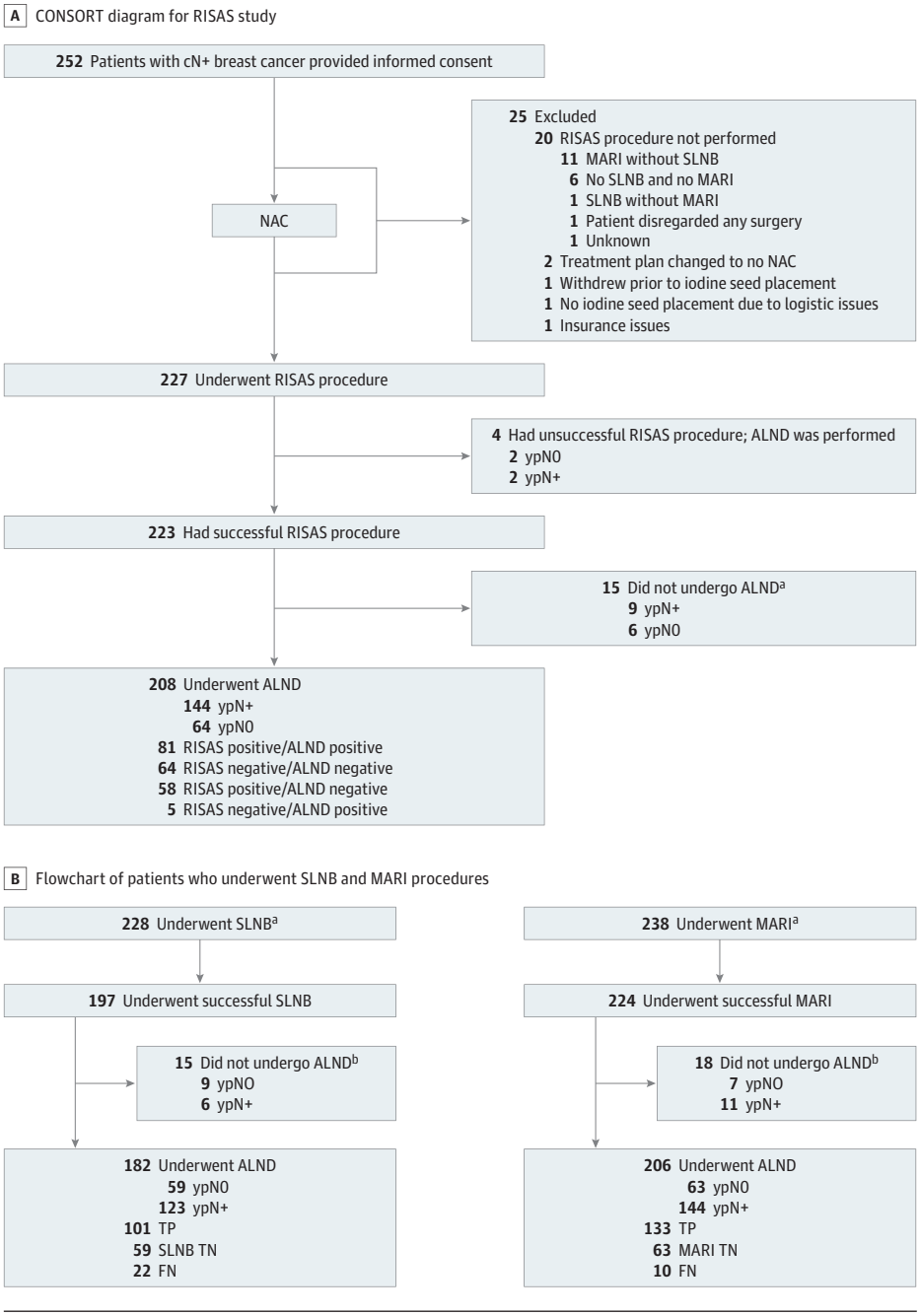
The FNR was defined as the number of FN results divided by the total number of patients with residual axillary disease, the sum of FN results plus true positive (TP) results = [FN / (FN + TP)]. The NPV was defined as the number of true negative (TN) results divided by the total number of patients with a negative test outcome = [TN / (TN + FN)]. An FN result occurred if the RISAS procedure incorrectly indicated axillary pCR (ie, the remaining lymph nodes of the ALND specimen did contain residual axillary disease).

The 1-sided McNemar exact test was used to test the null hypothesis that the FNR of the RISAS procedure was equal to the FNR of SLNB and of the MARI procedure. Statistical analysis was performed using the Statistical Package for the Social Sciences software, version 26 (IBM Corp). Data were analyzed from July 2020 to December 2021.

Results

A total of 252 patients provided informed consent from March 1, 2017, until December 31, 2019, of whom 227 patients underwent the RISAS procedure followed by completion ALND in 212 patients (median [range] age, 52 [22-77] years) (**Figure 1**A). The majority of patients had hormone receptor (HR)-positive/*ERBB2*-negative breast cancer (**Table 1**). The overall breast pCR (ypT0) rate was 30.5% (64 of 210), and the axillary pCR (ypN0) rate was 35.4% (75 of 212). Axillary pCR differed by subtype: 12.7% (13 of 102) for HR-positive/*ERBB2*-negative, 58.1% (25 of 43) for HR-positive/*ERBB2*-positive, 77.3% (17 of 22) for HR-negative/*ERBB2*-positive and 44.4% (20 of 45) for triple-negative breast cancer ($P < .001$).

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram and Flowchart



A, CONSORT diagram for the radioactive iodine seed placement in the axilla with sentinel lymph node biopsy (RISAS) procedure. B, Flowchart of patients who underwent sentinel lymph node biopsy (SLNB) and the marking of a pathologically confirmed positive axillary lymph node with radioactive iodine seed (MARI) procedure. In 3 of 9 patients with lymph node–negative (ypN0) status based on SLNB, residual disease was found in the MARI node. ALND indicates axillary lymph node dissection; cN+, clinically node positive; FN, false negative; NAC, neoadjuvant chemotherapy; TN, true negative; TP, true positive; ypN+, lymph node metastasis.

[a] At the patients' request, only the RISAS procedure without completion ALND was performed (this decision was always made before the surgical procedure took place).

[b] These numbers represent all patients in whom SLNB was performed (ie, RISAS procedure in 227 patients and SLNB only [without MARI] in 1 patient for a total of 228 patients for SLNB) or in whom the MARI procedure was performed (ie, RISAS procedure in 227 patients and MARI only [without SLNB] in 11 patients for a total of 238 patients for MARI).

RISAS Procedure

The RISAS procedure was successful in 223 of 227 patients (ie, at least 1 SLN and/or MARI node was identified), which resulted in an identification rate of 98.2%. The ALND specimen contained residual axillary disease in 2 of the 4 patients (50%) in whom the RISAS procedure was unsuccessful. A mean (SD) of 1.8 (1.1) lymph nodes was removed with the RISAS procedure (median [range], 2 [1-8] lymph nodes). In 35 of 223 patients (15.7%), either only the SLNB or only the MARI procedure was successful. In 188 of 223 patients (84.3%), both the SLNB and the MARI procedure were successful: the MARI node was also an SLN in 134 of 188 patients (71.3%). Residual axillary disease was located in either the SLN(s) or the MARI node in 19% of patients.

In 208 of 223 patients (93.3%) in whom the RISAS procedure was successful, completion ALND was performed, and these patients were included in the accuracy analysis (Figure 1A). Based on the on-site pathology evaluation of the RISAS lymph nodes, 73 patients had axillary pCR, 7 patients had an FN RISAS result, and 128 patients had residual axillary disease. Central pathology review was performed on the RISAS slides of the 80 patients with on-site axillary pCR in

the RISAS lymph nodes. Two patients did not have tissue available for additional sectioning. Central review revealed residual disease in 11 patients (based on revision of existing slides, n = 4; based on review of slides from additional sectioning, n = 7 [including 2 patients who initially had an FN RISAS result]). The residual disease consisted of macrometastasis in 1 patient (**Figure 2**) and isolated tumor cells and/or micrometastasis in the remaining patients. In all but 1 patient in whom central pathology review revealed residual disease, the lymph nodes showed signs of regression.

In summary, 64 patients had a TN result, 5 patients had an FN result, and 139 patients had a TP result after central pathology review. This yielded an FNR of 3.5% (5 of 144; 90% CI, 1.38-7.16) and an NPV of 92.8% (64 of 69; 90% CI, 85.37-97.10) (**Table 2**). The residual disease in the completion ALND consisted of macrometastasis in 4 patients (3 patients with 1 macrometastatic lymph node and 1 patient with 2 macrometastatic lymph nodes) and micrometastasis in 1 patient (in 2 lymph nodes). All FN results occurred in different institutions, and 4 of 5 FN results (80%) occurred within the first 10 included patients of the involved institutions. **Table 3** shows characteristics of patients with an FN result. In 81 of 139 patients (58.3%) with positive RISAS lymph nodes, the completion ALND specimen contained additional positive nodes.

The number of FN results was 2 for patients with cN1, 3 for patients with cN2, and 0 for patients with cN3b status. Owing to the small number of patients in these subgroups, FNR and NPV were not provided separately dependent on cN status.

SLNB

The SLNB was successful in 197 of 228 patients (86.4%). Sampling was performed with Tc 99m nanocolloid with or without blue dye in 215 of 228 (94.3%) patients (identification rate, 88.4% [190 of 215]). In the remaining 13 patients, sampling was performed with blue dye only (identification rate, 53.8% [7 of 13]). A total of 182 patients in whom SLNB was successful and completion ALND was performed were included in the accuracy analysis (Figure 1B). In 22 patients, no residual axillary disease was found in the SLN(s), whereas residual axillary disease was found in the nodes of the MARI procedure and/or completion ALND. This yielded an FNR of 17.9% (22 of 123; 90% 12.4%-24.5%) and an NPV of 72.8% (59 of 81; 90% 63.5%-80.4%) (Table 2).

One patient had lymph drainage to the contralateral axilla on lymphoscintigraphy and underwent bilateral axillary surgery; the contralateral SLN was tumor free, and the ipsilateral MARI node (which also appeared to be a hot node) contained a macrometastasis. In 17 of the 20 lymph nodes (85%) in the ipsilateral completion ALND specimen, macrometastases were found. One patient sustained an anaphylactic shock attributable to blue dye. A surgical procedure was performed successfully 2 weeks later, and the patient fully recovered from the adverse event.

MARI Procedure

In 224 of 238 patients (94.1%) the MARI procedure was successful. A total of 206 patients in whom the MARI procedure was successful and completion ALND was performed were included in the accuracy analysis (Figure 1B). In 10 patients, no residual axillary disease was found in the MARI lymph node, whereas residual axillary disease was found in the nodes of the SLNB and/or completion ALND. This yielded an FNR of 7.0% (10 of 143; 90% CI, 3.8%-11.6%) and an NPV of 86.3% (63 of 73; 90% CI, 77.9%-92.4%) (Table 2).

Table 1. Patient and Tumor Characteristics

Characteristic	No. (%)
All patients	212 (100)
Age, median (range), y	52 (22-77)
cT status[a]	
0	2 (0.9)
1	26 (12.3)
2	128 (60.4)
3	49 (23.1)
4	7 (3.3)
Multifocality	
No	158 (74.5)
Yes	54 (25.5)
cN status	
1	154 (72.6)
2	44 (20.8)
3b	14 (6.6)
Stage	
II	155 (73.1)
III	157 (26.9)
Subtype	
HR+/*ERBB2*−[b]	102 (48.1)
HR+/*ERBB2*+	43 (20.3)
HR−/*ERBB2*+	22 (10.4)
Triple negative	45 (21.2)
Type of breast surgery	
Lumpectomy	119 (56.1)
Mastectomy	93 (43.9)

Abbreviations: cN, clinical node status; cT, clinical tumor status; HR, hormone receptor.

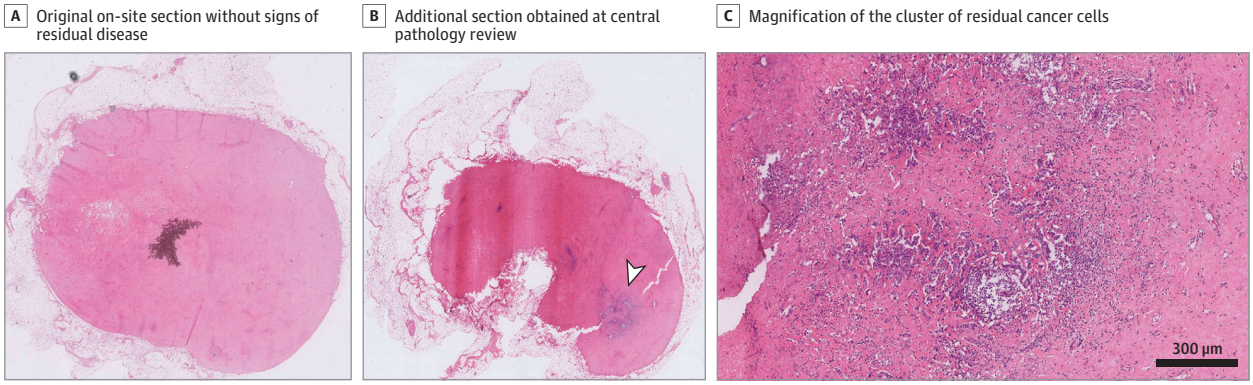
[a] cT status: 0, no evidence of primary tumor; 1, tumor is less than or equal to 2 cm in diameter; 2, tumor is greater than 2 cm but less than 5 cm in diameter; 3, tumor is greater than 5 cm in diameter; 4, tumor has extended to the chest wall or skin.

[b] Formerly *HER2* or *HER2/neu*.

Comparison of Accuracy of the RISAS Procedure With SLNB and the MARI Procedure

In 174 patients, both the SLNB and MARI procedure were successful and a completion ALND was performed. For this subgroup of patients, 56 patients (32.2%) had axillary pCR, and 118 patients (67.8%) had residual axillary disease. The FNR was 2.5% (3 of 118; 90% CI, 0.7%-6.4%) for the RISAS procedure, compared with 18.6% (22 of 118; 90% CI, 13.0%-25.5%; $P < .001$) for SLNB and 6.8% (8 of 118; 90% CI, 3.4%-11.9%; $P = .03$) for MARI (Table 2). The NPV was 94.9% (56 of 59) for the RISAS procedure, 71.8% (56 of 78) for SLNB, and 87.5% (56 of 64) for MARI.

Figure 2. Digital Hematoxylin and Eosin–Stained Tissue Sections From a Radioactive Iodine Seed Placement in the Axilla With Sentinel Lymph Node Biopsy (RISAS) Lymph Node That Underwent Central Pathology Review



A, The original on-site section without signs of residual disease. B, An additional section obtained at central pathology review with a large cluster (>2 mm) of residual cancer cells (arrowhead). C, Magnification of the cluster of residual cancer cells from panel (B).

Table 2. Identification Rate and Accuracy of the Radioactive Iodine Seed Placement in the Axilla With Sentinel Lymph Node Biopsy (RISAS) Procedure, Sentinel Lymph Node Biopsy (SLNB), and the Marking of a Pathologically Confirmed Positive Axillary Lymph Node With Radioactive Iodine Seed (MARI) Procedure[a]

Characteristic	No./total No. (%)		
	RISAS	SLNB	MARI
Whole cohort[b]			
Identification rate	223/227 (98.2)	197/228 (86.4)	224/238 (94.1)
FNR	5/144 (3.5)	22/123 (17.9)	10/143 (7.0)
NPV	64/69 (92.8)	59/81 (72.8)	63/73 (86.3)
Risk of missing residual disease when staging procedure indicates axillary pCR (1 in No. of patients)[c]	1 in 13.8 (69/5)	1 in 3.7 (81/22)	1 in 7.3 (73/10)
Subgroup analysis			
Identification rate	174/174 (100)	174/174 (100)	174/174 (100)
FNR[d]	3/118 (2.5)	22/118 (18.6)	8/118 (6.8)
NPV	56/59 (94.9)	56/78 (71.8)	56/64 (87.5)
Risk of missing residual disease when staging procedure indicates axillary pCR (1 in No. of patients)[c]	1 in 19.7 (59/3)	1 in 3.6 (78/22)	1 in 8.0 (64/8)

Abbreviations: FNR, false-negative rate; NPV, negative predictive value; pCR, pathologic complete response.

[a] Provided separately based on analysis of the whole cohort and based on analysis of a subgroup of patients within whom both the SLNB and MARI procedures were successful.

[b] Accuracy analysis for the RISAS procedure was based on 208 patients, for SLNB was based on 182 patients, and for the MARI procedure was based on 206 patients.

[c] Based on NPV rates of the different staging procedures.

[d] There was a statistically significant difference in FNR between the RISAS procedure and SLNB ($P < .001$) and between the RISAS and MARI procedures ($P = .03$).

Table 3. Characteristics of Patients With a False Negative Radioactive Iodine Seed Placement in the Axilla With Sentinel Lymph Node Biopsy (RISAS) Result (n = 5)

Age, y	Subtype	Clinical tumor status	Suspicious lymph node pre-NAC	Breast pCR
68	HR+/*ERBB2*−[a]	T2	<4	No
63	HR+/*ERBB2*−	T2	≥4	No
58	HR+/*ERBB2*+	T3	≥4	Yes
48	Triple negative	T2	≥4	No
51	Triple negative	T3	≥4	Yes

Abbreviations: NAC, neoadjuvant chemotherapy; pCR, pathologic complete response.

[a] Formerly *HER2* or *HER2/neu*.

Discussion

To our knowledge, this was the first prospective validation trial with a multicenter design, rather than a registry study, of patients with cN+ breast cancer who were treated with NAC. Results demonstrated that the RISAS procedure, a combination of SLNB and the MARI procedure, was associated with an FNR of 3.5% and an NPV of 92.8%. The upper bound of the confidence interval (2-sided 90% CI, 1.38%-7.16%) slightly exceeded the prespecified noninferiority margin of 6.25%, yet the difference was small, and therefore, it is expected that ALND added little to the detection of residual disease compared with the RISAS procedure. The RISAS procedure was associated with superior diagnostic accuracy compared with SLNB and MARI (FNR of 17.9% and 7% and NPV of 72.8% and 86.3%, respectively). Moreover, the RISAS procedure was associated with the highest identification rate of 98%; thus, only

2% of patients needed ALND to determine axillary treatment response. The results of the current trial corroborate results from previous studies, and the evidence is mounting that RISAS (ie, a targeted axillary dissection procedure) may be the preferred procedure to replace ALND for axillary staging.

In the current trial, results suggest that the RISAS procedure had 2 advantages over sole performance of either SLNB or MARI. First, the RISAS procedure was associated with an excellent identification rate of 98.2%. If only SLNB had been performed, approximately 15% of patients would have had no nodes identified and would have to undergo ALND to determine the axillary treatment response. The MARI procedure also had a lower identification rate than that of the RISAS procedure (94.1%). Second, the RISAS procedure was associated with improved accuracy, with a significantly lower FNR compared with SLNB and the MARI procedure. This was not only explained by the better identification rate; the MARI node may be tumor free, whereas the SLN harvests residual disease and vice versa. Reasons to explain this finding may include blockage of lymph drainage by residual tumor or a heterogeneous tumor response among axillary lymph nodes. The improved accuracy of procedures like RISAS is probably not simply attributable to the excision of more lymph nodes. The median number of lymph nodes excised with the RISAS procedure was only 2. Therefore, when SLNB is combined with MARI procedure, it is not necessary to harvest a minimum of 3 SLNs, in contrast to the separate SLNB.[16]

Axillary staging should not only serve to prevent unnecessary ALND in patients with an axillary pCR but also to accurately detect residual disease to guide adjuvant treatment decisions. The Trastuzumab Emtansine for Residual Invasive *ERBB2*-Positive Breast Cancer (KATHERINE)[17] and Adjuvant Capecitabine for *ERBB2*-Negative Breast Cancer After Preoperative Chemotherapy (CREATE-X)[18] trials showed that patients with residual disease may benefit from additional adjuvant systemic therapy (trastuzumab emtansine for *ERBB2*-positive and capecitabine for *ERBB2*-negative breast cancer) in terms of decreased risk of recurrence. Consequently, accurate assessment of treatment response is pivotal. Because the RISAS procedure was associated with the lowest FNR, it carries the lowest risk of missing residual disease (and thus the lowest risk of missing out on adjuvant systemic therapy).

It is unknown whether omission of ALND affects oncologic safety in terms of disease-free and overall survival. Several randomized controlled trials are currently assessing these end points, both for patients with axillary pCR (Axillary Management in Breast Cancer Patients With Needle Biopsy-Proven Nodal Metastases After Neoadjuvant Chemotherapy [ATNEC])[19] and B51/RTOG1304[20] trials) and for patients with residual disease (Alliance 011202[21] and Tailored Axillary Surgery With or Without Axillary Lymph Node Dissection Followed by Radiotherapy in Patients With Clinically Node-Positive Breast Cancer [TAXIS][22] trials). In the Netherlands, a prospective registry for patients with cN+ breast cancer treated with NAC is currently recruiting patients (the Minimal vs Maximal Invasive Axillary Staging and Treatment After Neoadjuvant Systemic Therapy in Node-Positive Breast Cancer [MINIMAX][23] trial). With the heterogenous application of less and more invasive axillary management strategies in daily practice,[24] this nationwide cohort allows for comparison between the different strategies in terms of survival as well as quality of life. Because ALND is already increasingly being omitted worldwide in patients with cN+ breast cancer treated with NAC,[25-27] these data are highly anticipated.

Limitations

This trial had a few limitations. Regarding central pathology review, the use of IHC on RISAS lymph nodes decreased the number of FN results, without substantially decreasing the number of TN results. However, in some patients, on-site IHC was performed, and therefore, the full effect of IHC cannot be determined within this trial. The participating institutions of the current trial had ample experience with iodine seed localization of breast lesions but little experience with localization of lymph nodes. Although these procedures are basically similar, institutions with vast experience in localizing lymph nodes may obtain better results (particularly because most of the FN results occurred within the first 10 included patients of the involved institutions). Nevertheless, the results of the MARI procedure within this trial correspond to data from the MARI trial itself, which reported an identification rate of 97% and FNR of 7%.[8] Regarding SLNB, the identification rate and accuracy of SLNB might have been better if dual-tracer technique was performed in all patients. Again, the findings of our trial correspond to data of a meta-analysis including 17 trials on SLNB, which reported an overall identification rate of 89% (range, 87%-92%) and overall FNR of 17% (range, 14%-20%).[1] Moreover, this study demonstrated that the RISAS procedure is clinically feasible in a multicenter setting, which supports implementation of this procedure in daily practice.

Conclusions

Results of this diagnostic study suggest that combining SLNB with excision of the marked lymph node may be the most accurate less-invasive procedure available for axillary staging after NAC in patients with cN+ breast cancer. Therefore, if less-invasive axillary staging is considered, the RISAS procedure (or a similar type of targeted axillary dissection), is clinically feasible in a multicenter setting, which supports implementation of this procedure in daily practice.

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